



LAHIVE  
&  
COCKFIELD  
L L P

COUNSELLORS AT LAW  
28 STATE STREET  
BOSTON, MASSACHUSETTS 02109-1784  
TELEPHONE (617) 227-7400  
FAX (617) 742-4214  
lc@lahive.com

JOHN A. LAHIVE, JR. (1928-1997)  
THOMAS V. SMURZYNSKI  
RALPH A. LOREN  
GIULIO A. DeCONTI, JR.  
ELIZABETH A. HANLEY  
AMY BAKER MANDRAGOURAS  
ANTHONY A. LAURENTANO  
KEVIN J. CANNING  
JANE E. REMILLARD  
DeANN FORAN SMITH  
DEBRA J. MILASINIC, Ph.D.  
WILLIAM A. SCOFIELD, JR.  
SIBBLEY P. REPPERT  
DAVID J. RIKKERS  
DAVID R. BURNS  
JOHN S. CURRAN  
SEAN D. DETWEILER  
MEGAN E. WILLIAMS, Ph.D.

LISA DIROCCO TYNER  
HATHAWAY P. RUSSELL  
MARIA LACOTRIPE ZACHARAKIS, Ph.D.  
MERIDETH C. ARNOLD  
DANIELLE L. HERRITT  
EUIHOON LEE \*\*  
MANEESH GULATI  
CYNTHIA M. SOROS  
PETER W. DINI, Ph.D.

SENIOR COUNSEL  
JAMES E. COCKFIELD

OF COUNSEL  
JEREMIAH LYNCH  
JEANNE M. DIGIORGIO  
CYNTHIA L. KANIK, Ph.D.  
JOHN D. LANZA

PATENT AGENTS  
THEODORE R. WEST  
JONATHAN M. SPARKS, Ph.D.  
ANDRINA WILLIAMS ZINK

TECHNICAL SPECIALISTS  
CATHERINE M. BISHOP  
JACOB G. WEINTRAUB  
CRISTIN E. HOWLEY, Ph.D.  
JILL ANN MELLO, Ph.D.  
DEBORAH L. NAGLE, Ph.D.  
ANNE JACQUELINE WIZEMAN, Ph.D.  
BRIAN C. TRINQUE, Ph.D.  
CHRISTOPHER R. COWLES, Ph.D.

\* Admitted in TX only  
\*\* Admitted in CT only

March 2, 2004

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Re: U.S. Patent Application No.: 10/681627  
For: *METHODS FOR MODULATING T CELL RESPONSES BY MANIPULATING INTRACELLULAR SIGNAL TRANSDUCTION*  
Inventor: June, Carl H.  
Filed: October 8, 2003  
Our Ref. No.: RPI-015DV

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Information Disclosure Statement;
2. PTO Form 1449; and
3. A Return Postcard.

No additional costs are believed to be due in connection with the filing of this Information Disclosure Statement. However, please charge any necessary fees in connection with the enclosed statement to our Deposit Order Account No. 12-0080. For this purpose, a duplicate of this sheet is attached.

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450:

March 2, 2004

Date

DeAnn F. Smith, Esq., Reg. No. 36,683

Respectfully submitted,  
LAHIVE & COCKFIELD, LLP

DeAnn F. Smith, Esq.  
Registration No. 36,683  
Attorney for Applicant



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: June, Carl H.

Serial No.: 10/681627

Filed: October 8, 2003

For: *METHODS FOR MODULATING T CELL  
RESPONSES BY MANIPULATING  
INTRACELLULAR SIGNAL TRANSDUCTION*

Attorney Docket No.: RPI-015DV

Group Art Unit: 1632

Examiner: Not Yet Assigned

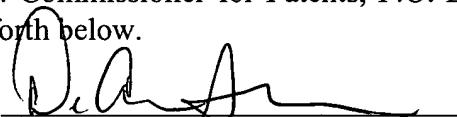
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Certificate of First Class Mailing (37 CFR §1.8(a))

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on the date set forth below.

March 2, 2004  
Date of Signature and of Mail Deposit

By:

  
DeAnn F. Smith, Esq.  
Registration No. 36,683  
Attorney for Applicant

INFORMATION DISCLOSURE STATEMENT

Dear Sir:

Applicant and his Attorney are aware of the following patents, publications or other information, which are cited on the attached PTO Form 1449, and in accordance with 37 CFR §1.97 hereby submit these publications for the Examiner's consideration.

The present application is a Divisional Application of U.S. Serial No. 08/245282, filed April 29, 1994 (Atty. Docket No. RPI-015). All references listed on the enclosed PTO Form 1449 have been previously cited by or submitted to the Office in the prior application, and, in accordance with 37 CFR §1.98(d), copies of these references are not enclosed herewith, but will be provided upon request.

This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any publication herein be construed *per se* as a representation that such publication is prior art. Moreover, Applicant understands that the Examiner will make an independent evaluation of the cited publications.

Under 37 CFR § 1.97(b)(3), no additional costs are believed to be due in connection with the filing of this disclosure. If, however, a first Office Action on the merits issues in this application bearing a mailing date prior to the date of this Information Disclosure Statement, please charge the appropriate fee as required under 37 CFR §1.17(p) to our Deposit Order Account No. 12-0080.

Respectfully submitted,  
LAHIVE & COCKFIELD, LLP



DeAnn F. Smith, Esq.  
Registration No. 36,683  
Attorney for Applicant

28 State Street  
Boston, MA 02109  
(617) 227-7400

Date: March 2, 2004

DFS/DLN/alf

APPLICANT FACSIMILE OF FORM PTO-1449  
REV 7-80U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTY DOCKET NO.

SERIAL NO.

RPI-015DV

10/681627

APPLICANT

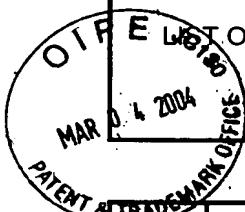
June, Carl H.

FILING DATE

GROUP

October 8, 2003

1632



U.S. PATENT DOCUMENTS							
EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	A1	5,504,103	04/96	Bonjouklian et al.	514	453	

## FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES      NO
	A2	WO 90/05541	05/90	PCT			

## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.)

A3		Abe, R. et al., "T Cell Receptor-mediated Recognition of Self-Ligand Induces Signaling in Immature Thymocytes before Negative Selection" <i>J. Exp. Med.</i> , Vol. 176, pp. 459-468, August 1992;
A4		Baggiolini, M. et al., "Inhibition of the Phagocytosis-Induced Respiratory Burst by the Fungal Metabolite Wortmannin and Some Analogues" <i>Experimental Cell Research</i> , Vol. 169, pp. 408-418, 1987;
A5		Blunden, G. et al., "Mycotoxins in food" <i>Medical Laboratory Sciences</i> , Vol. 48, pp. 271-282, 1991;
A6		Closse, A. et al., "2,3-Dihydrobenzofuran-2-ones: A New Class of Highly Potent Antiinflammatory Agents" <i>J. Med. Chem.</i> , Vol. 24, pp. 1465-1471, 1981;
A7		Gunther, R. et al., "Acute Pathological Effects on Rats of Orally Administered Wortmannin-Containing Preparations and Purified Wortmannin from <i>Fusarium Oryxsporum</i> " <i>Fd. Chem. Toxic.</i> , Vol. 27, No. 3, pp. 173-179, 1989;
A8		Gunther, R. et al., "Immunosuppressive Effects of Dietary Wortmannin on Rats and Mice" <i>Immunopharmacology and Immunotoxicology</i> , Vol. 11, No. 4, pp. 559-570, 1989;
A9		Harding, F.K. et al., "CD28-mediated signalling co-stimulates murine T cells and prevents induction of anergy in T-cell clones" <i>Nature</i> , Vol. 356, pp. 607-609, 16 April 1992;
A10		June, C.H., "Signal transduction in T cells" <i>Current Opinion in Immunology</i> , Vol. 3, pp. 287-293, 1991;
A11		June, C.H. et al., "Evidence for the Involvement of Three Distinct Signals in the Induction of IL-2 Gene Expression in Human T Lymphocytes" <i>J. Immunol.</i> , Vol. 143, No. 1, pp. 153-161, 1 July 1989;
A12		June, C.H. et al., "Role of the CD28 receptor in T-cell activation" <i>Immunology Today</i> , Vol. 11, No. 6, pp. 211-216, 1990;
A13		Ledbetter, J.A. et al., "CD28 Ligation in T-Cell Activation: Evidence for Two Signal Transduction Pathways" <i>Blood</i> , Vol. 75, No. 1, pp. 1531-1539, 1 April 1990;
A14		Ledbetter, J.A. et al., "Crosslinking of surface antigens cause mobilization of intracellular ionized calcium in T lymphocytes" <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 84, pp. 1384-1388, March 1987;

Examiner \_\_\_\_\_ Date Considered \_\_\_\_\_

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

APPLICANT FACSIMILE OF FORM PTO-1449  
REV 7-80U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTY DOCKET NO.

RPI-015DV

SERIAL NO.

10/681627

LIST OF PUBLICATIONS CITED BY APPLICANT  
(Use several sheets if necessary)

APPLICANT

June, Carl H.

FILING DATE

October 8, 2003

GROUP

1632

## OTHERS (including Author, Title, Date, Pertinent Pages, Etc.), Continued

		Lee, K. et al., "The CD28 Signal Transduction Pathway in T Cell Activation" in <i>Advances of Cell Regulation of Cell Growth, Volume 2 - Cell Activation: Genetic Approaches</i> , J.J. Mond et al. (eds.), New York: Raven Press, Ltd., pp. 141-160, 1991;
B2		Ley, S.C. et al., "The T cell receptor/CD3 complex and CD2 stimulate the tyrosine phosphorylation of indistinguishable patterns of polypeptides in the human T leukemic cell line Jurkat" <i>Eur. J. Immunol.</i> , Vol. 21, pp. 2203-2209, 1991;
B3		Lu, Yiling et al., "CD28-Induced T Cell Activation: Evidence for a Protein-Tyrosine Kinase Signal Transduction Pathway" <i>J. Immunol.</i> , Vol. 149, No. 1, pp. 24-29, 1 July 1992;
B4		Nunes, J. et al., "Signalling through CD28 T-cell activation pathway involves an inositol phospholipid-specific phospholipase C activity" <i>Biochem. J.</i> , Vol. 293, pp. 835-842, 1993;
B5		Okada, T. et al., "Blockage of Chemotactic Peptide-induced Stimulation of Neutrophils by Wortmannin as a Result of Selective Inhibition of Phosphatidylinositol 3-Kinase" <i>J. Biol. Chem.</i> , Vol. 269, No. 5, pp. 3562-3567, 4 February 1994;
B6		Okada, T. et al., "Essential Role of Phosphatidylinositol 3-Kinase in Insulin-induced Glucose Transport and Antilipolysis in Rat Adipocytes" <i>J. Biol. Chem.</i> , Vol. 269, No. 5, pp. 3568-3573, 4 February 1994;
B7		O'Shea, J.J. et al., "Activation of human peripheral blood T lymphocytes by pharmacological induction of protein-tyrosine phosphorylation" <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 89, pp. 10306-10310, November 1992;
B8		Pérez-Blas, M. et al., "Impaired T cell signal transduction through CD28 in a patient with idiopathic thrombocytopenia" <i>Clin. Exp. Immunol.</i> , Vol. 85, pp. 424-428, 1991;
B9		Prasad, K.V.S., et al., "Phosphatidylinositol (PI) 3-Kinase and PI 4-Kinase Binding to the CD4-p56 <sup>lck</sup> Complex: the p56 <sup>lck</sup> SH3 Domain Binds to PI 3-Kinase but Not PI 4-Kinase" <i>Molecular and Cellular Biology</i> , Vol. 13, No. 12, pp. 7708-7717, December 1993;
B10		Prasad, K.V.S., et al., "Src-homology 3 domain of protein kinase p59 <sup>fyn</sup> mediates binding phosphatidylinositol 3-kinase in T cells" <i>Proc. Natl. Acad. Sci. USA</i> , Vol. 90, pp. 7366-7370, August 1993;
B11		Schwartz, A., et al., "Quercetin Inhibition of the Induction and Function of Cytotoxic T Lymphocytes," <i>Immunopharmacology</i> , Vol. 4, pp. 125-138, 1982;
B12		Schwartz, R.H., "A Cell Culture Model for T Lymphocyte Clonal Anergy" <i>Science</i> , Vol. 248, pp. 1349-1356, 15 June 1990;
B13		Thompson, P.A., et al., "Identification of distinct populations of PI-3 kinase activity following T-cell activation" <i>Oncogene</i> , Vol. 7, pp. 719-725, 1992;
B14		Truitt, K.E. et al., "Stimulation of CD28 Triggers an Association between CD28 and Phosphatidylinositol 3-Kinase in Jurkat T Cells" <i>J. Exp. Med.</i> , Vol. 179, pp. 1071-1076, March 1994;
B15		Vandenberge, P. et al., "Antibody and B7/BB1-mediated Ligation of the CD28 Receptor Induces Tyrosine Phosphorylation in Human T Cells" <i>J. Exp. Med.</i> , Vol. 175, pp. 951-960, April 1992;
B16		Ward, S.G. et al., "Ligation of CD28 receptor by B7 induces formation of D-3 phosphoinositides in T lymphocytes independently of T cell receptor/CD3 activation" <i>Eur. J. Immunol.</i> , Vol. 23, pp. 2572-2577, 1993;

Examiner

Date Considered

\*EXAMINER:

Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

APPLICANT FACSIMILE OF FORM PTO-1448  
REV 7-80U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

ATTY DOCKET NO.

SERIAL NO.

RPI-015DV

10/681627

APPLICANT

June, Carl H.

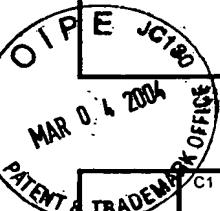
FILING DATE

October 8, 2003

GROUP

1632

**LIST OF PUBLICATIONS CITED BY APPLICANT**  
(Use several sheets if necessary)



OTHERS (including Author, Title, Date, Pertinent Pages, Etc.), Continued

C1		Ward, S.G. et al., "Regulation of D-3 phosphoinositides during T cell activation via the T cell antigen receptor/CD3 complex and CD2 antigens" <i>Eur. J. Immunol.</i> , Vol. 22, pp. 45-49, 1992;
C2		Ward, S.G. et al., "Regulation of Phosphoinositide Kinases in T Cells" <i>J. Biol. Chem.</i> , Vol. 267, No. 33, pp. 23862-23869, 25 November 1992;
C3		Ward, Stephen G. et al. "Inhibition of CD28-mediated T cell costimulation by the phosphoinositide 3-kinase inhibitor wortmannin" <i>Eur. J. Immunol.</i> Vol. 25, pp. 526-532, 1995;
C4		Wiesinger, D. et al., Antiinflammatory Activity of the New Mould Metabolite 11-Desacetoxy-Wortmannin and Some of its Derivatives" <i>Experientia</i> , Vol. 30, pp. 135-136, 1974;
C5		Wu, W. and C.J. Mirocha, "Decreased Immunological Responses by Wortmannin-Containing Rice Culture of <i>Fusarium Oryxsporum</i> and by Purified Wortmannin in Avian Species" <i>Immunopharmacology and Immunotoxicology</i> , Vol. 14, No. 4, pp. 913-923, 1992;
C6		Wu, W. and Mirocha, C.J., "Wortmannin (A Mycotoxin) Inhibited Immune Responses in Chickens," <i>Poultry Science</i> , Vol. 71, suppl. 1, p. 13, 1992;
C7		Yang, S.Y. et al., "A Novel Activation Pathway for Mature Thymocytes" <i>J. Exp. Med.</i> , Vol. 168, pp. 1457-1468, October 1988;
C8		Yano, H. et al., "Inhibition of Histamine Secretion by Wortmannin through the Blockade of Phosphatidylinositol 3-Kinase in RBL-2H3 Cells" <i>J. Biol. Chem.</i> , Vol. 268, No. 34, pp. 25846-25856, 5 December 1993;
C9		Yoshida, M., et al., "Quercetin Arrests Human Leukemic T-Cells in Late G <sub>1</sub> Phase of the Cell Cycle," <i>Cancer Research</i> , Vol. 52, pp. 6676-6681, 1992.
Examiner		Date Considered
*EXAMINER:	Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	